RESEARCH ARTICLE

A STUDY ON DRUG UTILIZATION PATTERN IN PATIENTS OF DIABETIC NEPHROPATHY WITH PROTEINURIA AT A TERTIARY CARE CENTRE IN SOUTHERN INDIA

Kishan PV[1], Bondalapati Sowmya[2], **Banerjee Prithwijit[3]***, Ramanujam N[4], Rai Shivali[5], Dan Subhasish[6]

[1]DM resident, Department of Clinical Pharmacology and Therapeutics, NIMS, Hyderabad, India

[2]MBBS, Post graduate trainee, Department of Internal Medicine, Mamata Medical College, Khammam, India

[3]MD, Demonstrator, Department of Pharmacology, Medical College Hospital, Kolkata, India

[4]MD, Assistant Professor, Department of Pharmacology, PSG Institute of Medical Sciences and Research, Coimbatore, India

[5]MD, Assistant Professor, Department of Pharmacology, Saveetha Medical College, Chennai, India

[6]MD, Demonstrator, Department of Biochemistry, Medical College Hospital, Kolkata, India

Corresponding Author's e-mail: drprithwijit@gmail.com, Contact no: +91-9830500513

ABSTRACT

Background and objective: Incidence and prevalence of Diabetes in developing countries like India is on the rise. Diabetic nephropathy is one of the commonest causes of proteinuria associated with renal disorder and creates a sound socio-medical and pharmacoeconomic basis for healthcare decision making. The principal aim of this research is to facilitate rational use of drugs in the patient population suffering from Diabetic nephropathy. **Materials and methods:** We collected the data from 313 Diabetic patients who got admitted in the Department of Nephrology from June 2009 to December 2010 with proteinuria on urine analysis and the drug utilization pattern was analyzed statistically. **Result:** Based on our observation, Renin Angiotensin Aldosterone System (RAAS) inhibitors like ACEIs and ARBs are the most frequently used agents in case of Diabetic nephropathy with proteinuria besides the anti diabetic therapy. Among those, ARBs are more commonly prescribed than ACEIs. **Conclusion:** Early detection of nephropathy and the use of reno-protective agents like ARBs and or ACE inhibitors, may delay the progression of renal disease in Diabetic patients besides reducing the cardiovascular morbidity and mortality.

Keywords: Diabetic nephropathy, ACE inhibitors, ARB, Diuretics, Oral Anti Diabetics, Proteinuria, Renin Angiotensin Aldosterone System

INTRODUCTION

Diabetic nephropathy is a spectrum of progressive renal lesions secondary to diabetes mellitus ranging from renal hyper filtration to end stage kidney disease and responsible for significant morbidity and mortality among the Diabetic population[1]. It occurs as a microvascular complication of both insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetes mellitus characterised by persistent proteinuria, decline in glomerular filtration rate (GFR)[2]. The overall prevalence of diabetic nephropathy varies from 20 - 40% in diabetic patients[2]. It occurs in 30% of type I diabetics, 5 to 15 years after diagnosis but may be present at diagnosis in type II diabetics, as the time of onset of type II diabetes is often unknown[1]. Diabetic nephropathy is also the most common cause of end stage renal disease (ESRD) and has a devastating impact on morbidity and mortality of patients with diabetes mellitus[1].

Known risk factors for the development of diabetic nephropathy include genetic predisposition, poor glycaemic control, hypertension and smoking[1]. Prevention, early detection and aggressive intervention are needed to retard the progression of diabetic nephropathy to end stage renal failure[1,2].

The earliest clinical evidence of nephropathy is the presence of microalbuminuria.. Microalbuminuria progresses to overt proteinuria over the next 7 to 10 years. Once overt proteinuria develops, renal function progressively declines and end stage renal failure is reached after about 10 years[1,2]. Microalbuminuria is a powerful and independent predictor of cardiovascular death[3].

The management of diabetic nephropathy includes good glycaemic control, tight control of blood pressure and reduction of proteinuria with cessation of smoking, lipid control and salt and protein restriction[4]. Therapeutic intervention is intended to prevent or retard the progression of diabetic renal disease as well as to reduce cardiovascular complications[4].

Independent of their antihypertensive effect, reno protective agents like ACEIs[5] (Angiotensin Converting Enzyme inhibitors) and ARBs[6] (Angiotensin receptor blokers) have been shown to reduce microalbuminuria as well as overt proteinuria, associated with Diabetes. Landmark clinical trials of ACEIs in type I [7] and ARBs in type II [8] diabetics have clearly demonstrated the effectiveness of these agents to retard the progression of overt diabetic nephropathy. Therefore, ACEIs and ARBs should be instituted even in the settings of moderately severe renal failure[9].

Several small studies have indicated that the combination of ACEI and ARB may have additive effect in lowering

blood pressure and proteinuria in diabetic patients with microalbuminuria and overt nephropathy[10].

Drug utilization studies are conducted frequently all over the world. In developing countries with the constraint of health budget for drugs, it becomes even more meaningful to prescribe drugs rationally. These studies can thus help to set priorities for the rational allocation of health care budgets and can ascertain the role of drugs in society. The present study was undertaken in a tertiary care hospital to evaluate the current drug utilization pattern in patients with Diabetic nephropathy and to facilitate rational use of drugs in such patient population.

MATERIALS AND METHODS

The study began after the approval from the Institutional Ethics Committee. Data was collected from 313 case sheets of Diabetic patients, who got admitted in Nephrology department at Sri Ramachandra Hospital, Chennai, from June 2009 to December 2010 with proteinuria on urine analysis. Later, the detailed analysis of drug utilization pattern was performed statistically.
However, we did not include pregnant and lactating mothers and the patients who are on hemodialysis support.
Patients attending outdoors were not considered either.
This study was a non interventional observation in nature.

RESULTS:

From the demographic details (Table 1), male sex appeared to be affected more than female with Diabetic nephropathy (63.2% versus 36.8%). A significant number of patients also had co morbidities like Hypertension (76.9%), Dyslipidemia (61.3%) and Obesity (39.3%).

Table 1: Demographic details of all the patients

Total patients	313
Male	198 (63.2%)
Female	115 (36.8%)
Mean age (years)	37.6 ± 24.7
Mean duration of disease (years)	12.6 ± 4.2
Smokers	208 (66.5%)
Type 1 DM cases	135 (43.1%)
Type 2 DM cases	178 (56.9%)
Associated Hypertension	241 (76.9%)
Associated Dyslipidemia	192 (61.3%)
Associated obesity	123 (39.3%)

There was lesser number of patients of Type1 DM than Type 2 in our study.

Table 2: Details of the drug utilization pattern

Classes of Drugs with examples	Percentage of patients received the drug*
ACE inhibitor (Enalapril, Ramipril)	32%
ARB (Losartan, Telmisartan, Olmesartan)	68%
CCB (Amlodipine, Cilnidipine)	48%
Diuretics (Hydrocholorthiazide)	55%
Statins (Atorvastatin, Rosuvastatin)	63%
(Insulin and/or OHAs)	100%

**Rounded off to nearest whole number*

Insulin and or oral hypoglycemic agents were universally prescribed among all the patients as anti diabetic therapy (Table 2). Similarly, all of them received at least one drug that inhibits RAAS (Renin Angiotensin Aldosterone system) in the form of ACE inhibitors (32%) or ARBs (68%). Diuretics and CCBs were prescribed in 55% and 48% respectively.

Table 3: Dosage and frequency of administration of individual drugs

Drug	**Most frequently prescribed dose**	**Maximum prescribed dose**
Enalapril	5 mg BD	20mg BD
Ramipril	2.5mg OD	10mg OD
Losartan	50mg OD	50mg BD
Telmisartan	40mg OD	80mg OD
Olmesartan	20mg OD	40mg OD
Hydrochlorothiazide	12.5mg OD	25mg OD
Amlodipine	5mg OD	20 mg OD
Cilnidipine	10mg OD	20mg OD
Atorvastatin	10mg OD	40mg OD
Glimepiride	2mg OD	6mg OD
Glipizide	10mg OD	20mg OD

OD: once daily, BD: twice daily

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 4: Most frequently utilized agents from different drug classes

Drug class	Percentage of usage
ACE inhibitors	Ramipril (58%), Enalapril (42%)
ARBs	Losartan (44%), Telmisartan (39%), Olmesartan (17%)
CCBs	Amlodipine (84%), Cilnidipine (16%)
Statins	Atorvastatin(76%),Rosuvastatin (14%)
Sulfonylurea	Glimepiride (69%), Glipizide (31%)

**Rounded off to nearest whole number*

Table 5: Fixed dose combination therapy used in Diabetic nephropathy

Drug combination	Examples
ARB + Diuretics	Losartan(50mg) + Hydrochlorothiazide(12.5mg) Telmisartan(40mg) + Hydrochlorothiazide(12.5mg)
ARB + CCB	Losartan(25/50mg) + Amlodipine (5mg) Telmisartan(40/80mg) + Amlodipine (5mg) Olmesartan (20/40mg) + Amlodipine (5mg) Telmisartan(40mg) + Cilnidipine (10mg)
ARB + CCB + Diuretics	Losartan(50mg)+Amlodipine(5mg)+Hydrochlorothiazide(12.5mg) Telmisartan(40mg)+Amlodipine(5mg)+Hydrochlorothiazide(12.5mg) Olmesartan(20mg)+Amlodipine(5mg)+Hydrochlorothiazide(12.5mg)
ACE inhibitors + Diuretics	Enalapril(5mg) + Hydrochlorothiazide(12.5mg) Ramipril(2.5/5mg) + Hydrochlorothiazide(12.5mg)
Statin + Fibrate	Atorvastatin (10mg) + Fenofibrate (160mg) Rosuvastatin (10mg) + Fenofibrate (160mg)

Table 6: Physician's Advice

Physician's advice	Percentage
Anti Diabetic diet	25%
Protein restriction	85%
Salt restriction	60%
Avoid Nephrotoxic drugs	25%
Physical exercise	30%

DISCUSSION

A changing life style in developing countries like India has enormously increased the statistical figures of chronic diseases like diabetes mellitus, hypertension and chronic kidney disease[11]. One of the most common causes of renal disorders associated with proteinuria in our tertiary care hospital is Diabetic nephropathy.

Table 1 implies that 63.2 % of patients are males. The reason could be increased smoking habit found among men in India, which would have accelerated the progression of Diabetic and non-diabetic renal disease[12]. In fact 66.5% of patients here had a positive smoking history. Close association with Hypertension, Dyslipidemia and Obesity was also evident.

Type II DM constituted more number of cases than type I here (56.9% vs. 43.1%). This is probably because of early diagnosis and initiation of therapy in the latter, where patients become symptomatic much before than type II.

Since a tight glycemic control is the most important factor to halt the process of nephropathy, all patients were given anti diabetic therapy with either Oral hypoglycemic agents and or Insulin (Table2). Different forms of Insulin were prescribed on the basis of patient's requirement, while Glimepiride appeared to be the most commonly used oral agent.

Due to their established efficacy in Diabetic nephropathy, ACEIs (32%) and ARBs (68%) were the two most frequently utilized drugs in this setup[5,6]. In our study there was practically no patient, who did not get at least one drug from these two groups.

In type I diabetic patients with or without hypertension, ACEIs have been shown to reduce microalbuminuria[5], while in type II diabetics, ACEIs and more recently ARBs have been shown to reduce microalbuminuria[6].

Clinical trials involving ACEIs and ARBs in Diabetic nephropathy have shown significant reductions in the risk of doubling of plasma creatinine and developing renal failure. These benefits were independent of blood pressure lowering[7, 8].

There is also clinical evidence regarding the initiation of ACEIs or ARBs even in the settings of moderately severe renal failure. Although, the renal function should be carefully monitored in those patients[9].

According to a trial done by Brenner, Parving et al, ARBs are better than ACE inhibitors in reno-protection beyond blood pressure control[8]. ARB may produce reno-protective benefits by lowering the fibrogenic cytokine Transforming Growth Factor-β (TGF β), reducing proteinuria, decreasing renal oxidative stress, preserving glomerular and tubulointerstitial structure and reducing the glomerular membrane pore size[6,8].

The choice between ACEIs and ARBs depends on the followings conditions; [13]

- In hypertensive Type I diabetic patients with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.
- In hypertensive Type II diabetic patients with microalbuminuria, ACE inhibitors and ARBs have shown to delay the progression.
- In patients with Type II diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been shown to delay the progression of nephropathy.

ACEIs and ARBs should be used with caution in patients with bilateral renal artery stenosis or renal artery stenosis of a single functioning kidney. ACEIs and ARBs should be started at lower doses in renal failure and titrated gradually to maximal tolerable dose to achieve anti-proteinuric effect. Serum potassium and creatinine should be checked prior to and within one to two weeks after initiating an ACEI or ARB as they can occasionally cause worsening of renal function[13].

Diuretics potentiate the antihypertensive and anti-proteinuric effect of ACEIs and ARBs[14]. This explains why Hydrochlorothiazide was prescribed in 55% of our patients.

We also found Calcium channel blockers (CCBs) like Amlodipine and Cilnidipine to be other commonly prescribed agents (table 2), as they have some class specific effect on proteinuria. However, the effect may be variable with different Dihydropyridines (e.g. nifedipine, amlodipine) [15]. Recently, there are clinical evidences in favour of anti proteinuric effect of Cilnidipine[16]. In our study, it was the second commonest CCB used after Amlodipine (Table 4).

Treatment of hyperlipidemia with lipid lowering drugs like Atorvastatin, smoking cessation, dietary protein restriction, salt restriction also play a major role in halting the progression of diabetic nephropathy. Very recent study has proved the role of Atorvastatin in reduction of renal cholesterol synthesis in rat[17].

Table 5 demonstrates the combination drug therapy used in our tertiary care hospital for diabetic nephropathy. The multifactorial etiologies of the disease suggest that multi-interventional approach is mandatory to halt the progression of renal disorders and for the reversal of renal microvascular complications. Drugs from two or more groups are often combined for this purpose. We observed that ARBs with Diuretics or CCBs are the most frequently utilized drug combination.

Table 6 shows the physicians' advice given to the patient with renal disorders associated with proteinuria. Majority of them were advised protein restricted diet and salt restriction. A study by Koya et al has shown that a low-protein diet could prevent the progression of diabetic nephropathy[18].

CONCLUSION

Early detection of renal disorders and the adoption of multifactorial interventions targeting the main risk factors (Hypertension, Hyperglycemia, Dyslipidemia, Smoking) and the use of reno-protective agents such as ARBs and or ACEIs, may delay the progression of renal disease besides reducing the cardiovascular morbidity and mortality.

From our study, it shows that the most commonly prescribed drugs in patients suffering from Diabetic nephropathy with proteinuria are ARBs and ACE inhibitors beside the anti diabetic therapy. Among those, ARBs are more frequently prescribed than ACE Inhibitors.

Combination therapy of drugs was prescribed owing to the multifactorial etiology and pathogenesis of the disease. ARB with Diuretics or CCBs appeared to be the most commonly prescribed combination therapy.

Conflict of interest: There was nothing to the best of our knowledge so far.

REFERENCES:

1. Ranjith unnikrishnan, Mohan rema, Rajendra pradeepa M, Mohan deepa M. Prevalence and Risk Factors of Diabetic Nephropathy in an Urban South Indian. The Chennai Urban Rural Epidemiology Study (CURES 45) Blood Pressure. 2007 ;30(8):2019-24.
2. Clinical Practice Guidelines: Diabetic Nephropathy. July 2004(Ministry of health, Malaysia) p.1-38.
3. Meisinger C, Heier M, Landgraf R, Happich M, Wichmann H, Piehlmeier W. Albuminuria , cardiovascular risk factors and disease management in subjects with type 2 diabetes : a cross sectional study. BMC Health Services Research. 2008 ;71-77.
4. Perkovic V, Verdon C, Ninomiya T, Barzi F, Cass A, Patel A, et al. The Relationship between Proteinuria and Coronary Risk : A Systematic Review and meta-analysis. PLoS Medicine. 2008;5(10):1486-95.
5. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICROHOPE substudy. *Lancet* 2000;355(9200):253-9.
6. Bichu P, Sowers JR, Whaley-connell A. Angiotensin receptor blockers for the reduction of proteinuria in diabetic patients with overt nephropathy : results from the AMADEO study. Vascular Health And Risk Management. 2009 ;5:129-40.
7. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD for The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329(20):1456-62
8. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345(12):861-9.
9. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345(12):851-60.
10. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ. 2000 ;321:440-44.
11. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates and projections. Diabetes Care 1998; 21:1414-31.
12. Al Nasser et al, Health care in PARK – Text book of Community medicine.17th ed. 2002. p 685-6.
13. Zelmanovitz T, Canani LH, Gross JL, Silverio SP. Diabetic nephropathy: Diagnosis, Prevention, and Treatment. Diabetes care 2005;28:164-76.
14. Flack JM. Maximising antihypertensive effects of angiotensin II receptor blockers with thiazide diuretic combination therapy : focus on irbesartan / hydrochlorothiazide. Int J Clin Pract,. 2007 ;61(12):2093-102.
15. Demarie BK, Bakris GL. Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. *Ann Intern Med* 1990;113(12):987-8.
16. Shunichi KOJIMA, Mikio SHIDA, and Hiroyuki YOKOYAMA. Comparison between Cilnidipine and Amlodipine besilate with respect to proteinuria in hypertensive patients with renal disease. *Hypertens Res*, 2004; 27: 379–385.
17. Hong Sung, Yang Yuan and Zi-Lin Sun. Cholesterol contributes to Diabetic nephropathy through SCAP-SREBP2 pathway, *Int J of Endocr*,2013;1; 1-9.
18. Koya D, Haneda M, Inomata S, Suzuki Y. Long-term effect of modification of dietary protein intake on the progression of diabetic nephropath : a randomised controlled trial. Diabetologia. 2009 ;53:2037-45.

.

